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Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management

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Abstract

Iron deficiency, even in the absence of anemia, can be debilitating, and exacerbate any underlying chronic disease, leading to increased morbidity and mortality. Iron deficiency is frequently concomitant with chronic inflammatory disease; however, iron deficiency treatment is often overlooked, partially due to the heterogeneity among clinical practice guidelines. In the absence of consistent guidance across chronic heart failure, chronic kidney disease and inflammatory bowel disease, we provide practical recommendations for iron deficiency to treating physicians: definition, diagnosis, and disease-specific diagnostic algorithms. These recommendations should facilitate appropriate diagnosis and treatment of iron deficiency to improve quality of life and clinical outcomes.

*"Iron deficiency is very common but often overlooked, especially in people with chronic conditions. Iron deficiency is a health-related condition in which iron availability is insufficient to meet the body's needs and, therefore, its timely detection and treatment is important, because iron is essential to the functioning of all organs"*¹

1 | INTRODUCTION

Managing patients with chronic diseases, particularly those with complex inflammatory disorders, can be challenging. In these patients, a considered multidisciplinary approach needs to be adopted to maintain quality of life (QoL) and improve outcomes.^{2,3} One condition that is frequently associated with chronic disease, but often overlooked, is iron

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deficiency. Iron deficiency is estimated to affect 37–61% of patients with chronic heart failure (CHF), 24–85% of patients with chronic kidney disease (CKD) and 13–90% of patients with inflammatory bowel disease (IBD).^{4–9} Iron is essential to every cell and, while its fundamental role in oxygen transport through erythropoiesis is well recognized, it is equally critical for energy production and efficient functioning of all of the body's organs.^{10,11} In patients with chronic inflammatory conditions, its impact can be particularly severe and may exacerbate the underlying disease state, leading to accelerated clinical deterioration.^{5,12}

Anemia is the ultimate consequence of iron deficiency in many patients with chronic inflammatory conditions.^{2,3,13,14} However, the medical field should recognize iron deficiency as a clinical condition distinct from anemia. Recognition is improving owing to our better understanding of the pathophysiological role of iron deficiency (independent of chronic anemia) in symptomatology and clinical outcomes.^{10,15,16} This is further supported by recent clinical observations of an association between the alleviation of morbidity or mortality and the treatment of iron deficiency, even outside the context of anemia.^{6,17,18} However, there is uncertainty among physicians on how to diagnose iron deficiency in patients with chronic inflammatory conditions. This is partially because of symptom overlap with the underlying disease and unclear laboratory diagnostic thresholds. Several publications have also highlighted the problems of recognizing iron deficiency in the context of anemia of inflammation.^{13,19–21} This has led to under-diagnosis of an easily treatable condition, leading to anemia, at which point physicians feel more confident about using iron therapy.²²

In part, this uncertainty also stems from the heterogeneity of guideline recommendations for the diagnosis and management of iron deficiency in chronic inflammatory diseases. In the absence of any overarching guidance, a series of roundtable discussions were convened to try and bridge this gap. Our objectives were to: (1) provide a definition of iron deficiency; (2) examine the current evidence on (and identify knowledge gaps in the clinical impact of iron deficiency in chronic inflammatory conditions, specifically CHF, CKD, and IBD; and (3) provide practical guidance for the diagnosis of iron deficiency in these patient populations.

1.1 | Mechanisms of iron deficiency in chronic inflammation

Iron plays an important role in many physiological processes.¹⁵ All aspects of iron homeostasis are tightly controlled and regulation of iron transport is central to this process.^{10,23} The hepatic peptide hormone hepcidin and its transmembrane receptor, ferroportin, control the principal routes of iron transport and availability in the body.¹⁵ Hepcidin levels are feedback regulated by plasma iron concentration and the amount of iron stores.¹⁵ Levels are also negatively regulated by the activity of erythrocyte precursors, the main consumers of iron.¹⁵ Hepcidin controls the internalization and degradation of ferroportin, which transfers cellular iron into the plasma and is predominantly expressed in key iron exporters (eg, enterocytes and iron-recycling macrophages).^{10,16}

Hepcidin, and therefore the regulation of ferroportin, is affected by inflammation (Figure 1).^{15,24,25} In inflammatory conditions, hepcidin production and release is induced by circulating proinflammatory

cytokines, especially interleukin-6. This results in increased internalization and degradation of ferroportin and subsequent cellular iron retention. This ultimately leads to decreased levels of circulating iron, which may result in insufficient iron availability to meet the body's needs.^{10,15,16}

It is estimated that for the healthy individual, total body iron content is ~3–4 g, of which 1–2 mg of exogenous iron is absorbed per day and 25 mg of iron is required daily for erythropoiesis, mostly obtained from iron recycling.²⁶ As a result of limited iron supply from macrophage-led iron retention, patients with chronic inflammatory conditions have greater daily iron requirements to increase the levels of circulating iron compared with healthy individuals.^{27–29} As a consequence of severely depleted iron availability, proper functioning of many organ systems is compromised in these patients.^{27–29} For example, iron content and transferrin receptor levels were decreased in the myocardium of patients with iron deficiency anemia and advanced heart failure compared with healthy individuals, suggesting that iron depletion was associated with adverse outcomes in these patients.³⁰

1.2 | Defining iron deficiency

Based on our literature review, it is evident that iron deficiency is not fully recognized as a disorder distinct from iron deficiency anemia, or as one that may have its own clinical consequences. Indeed, the terms “iron deficiency” and “iron deficiency anemia” are often used interchangeably.³¹ Where iron deficiency is discussed, it is frequently perceived as the most common nutritional disorder worldwide,^{31–33} but not as a medical condition in and of itself.³⁴

It is clear that the heterogeneity in how iron deficiency is defined is a knowledge gap that is compounding physicians' lack of confidence in recognizing and diagnosing this condition. The lack of a standard simple definition for iron deficiency hinders its uncoupling from iron deficiency anemia and its acceptance as a standalone medical condition with distinct clinical implications.

1.3 | Expert recommendation

We propose the following wording as an overarching definition of iron deficiency:

Iron deficiency is a health-related condition in which iron availability is insufficient to meet the body's needs and which can be present with or without anemia

1.4 | Clinical impact of iron deficiency

Iron deficiency may contribute to several symptoms that can manifest even in the absence of progression to anemia. Although there are symptoms that are likely to be caused by iron deficiency (eg, pagophagia, and RLS), many symptoms are nonspecific, such as fatigue, and exhaustion.^{35–38} This means that physicians and patients do not always

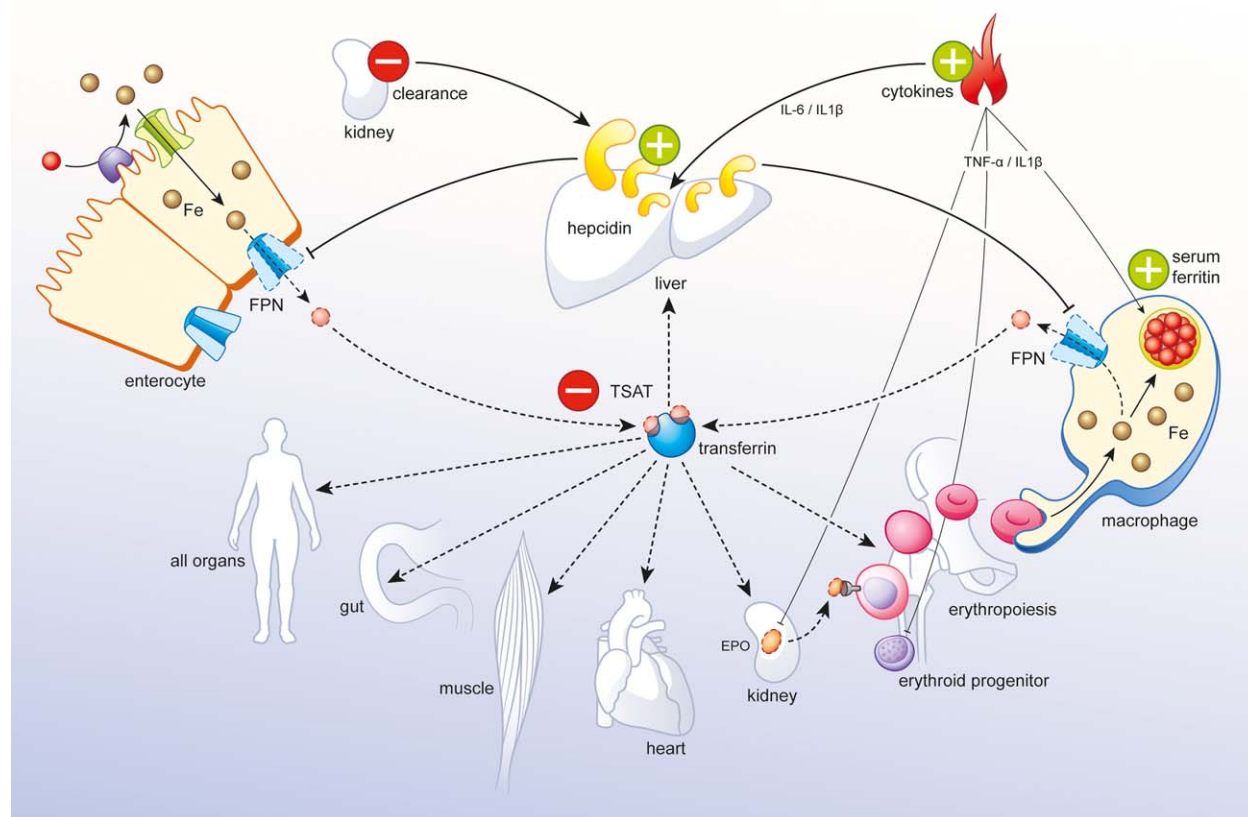


FIGURE 1 The pathophysiology of iron deficiency in chronic inflammation. Increased cytokine levels in all conditions, and decreased renal clearance in CKD and CHF, result in enhanced hepcidin levels. High hepcidin levels bind, internalize and degrade ferroportin on the lateral membrane of duodenal enterocytes and spleen macrophages. Iron remains trapped in enterocytes, which are then shed in the gut. Iron is also sequestered into macrophages, which are responsible for destroying senescent red blood cells and recycling their iron. Serum ferritin levels are regulated by the iron content of macrophages and increase in inflammation (apo ferritin as an acute-phase protein). A decrease in circulating iron leads to lower amounts of iron bound to the iron carrier protein, transferrin, and subsequently to a decline in transferrin saturation and low iron supply to all organs. Furthermore, cytokines may also have negative effects on erythropoietin production in the kidney and erythroid cell maturation, while also increasing macrophage iron retention. Note that the increased iron losses that can occur in specific chronic inflammatory conditions are not illustrated here. Plus and minus signs represent increase/enhancement and decrease, respectively. EPO, erythropoietin; FPN, ferroportin; IL, interleukin; TNF, tumor necrosis factor; TSAT, transferrin saturation

recognize that iron deficiency is present and, as a consequence, diagnosis is not pursued and the condition is left untreated.

Physicians may need to actively ask their patients about such symptoms, especially for those patient populations where iron deficiency is highly prevalent, so that appropriate diagnostic tests can be performed and, if necessary, treatment can be given.³⁵ In this section, we outline the iron deficiency symptoms that have been commonly reported in patients with CHF, CKD and IBD, as well as its associated clinical outcomes that further call for its prompt diagnosis and management.

1.5 | Iron deficiency in chronic heart failure

Iron deficiency is estimated to affect between 37 and 61% of patients living with CHF, and its prevalence increases as CHF advances.^{5-7,9} The etiology of iron deficiency in CHF is not fully understood, but it is

thought to be multifactorial and arising from: a general loss of appetite and poor nutrition; decreased gastrointestinal (GI) iron absorption due to edema; increased GI blood loss that may occur partially as a result of antiplatelet and anticoagulant drugs; and, importantly, as a consequence of the chronic inflammatory state of these patients.^{28,39} The diagnosis of iron deficiency in CHF is complicated by the fact that the key manifestations of CHF (fatigue, exercise intolerance) are the same as those of iron deficiency. Fatigue is frequently associated with iron deficiency in CHF patients and linked with reduced exercise and work capacity.⁴⁰⁻⁴³ In a recent study using the 6-min walk test (6MWT), exercise-induced symptoms were significantly more frequent in iron-deficient CHF patients (35%) compared with non-iron-deficient patients (27%; $P = 0.028$); the most commonly reported symptom was fatigue.⁴⁴

In CHF, iron deficiency has been shown to adversely impact exercise capacity and QoL independently of anemia. Iron deficiency

significantly reduces exercise tolerance as measured by the 6MWT.^{17,44–46} In the FAIR-HF study, iron-deficient CHF patients who were treated for iron deficiency with intravenous (IV) iron, ferric carboxymaltose, had significant improvements in the 6MWT ($P < 0.001$ at weeks 4, 12, and 24) compared with those receiving placebo.⁴⁵ These findings are supported in the recent EFFECT-HF study, whereby treatment with ferric carboxymaltose led to significant improvement in exercise capacity in iron-deficient CHF patients compared with other standard treatments other than IV iron.⁴⁷ In a secondary analysis, the same patients experienced significantly increased QoL as measured by the Kansas City Cardiomyopathy questionnaire ($P < 0.001$).⁴⁵ Studies demonstrated that QoL was significantly affected by iron deficiency in patients with CHF, whether assessed using the European Quality of Life-5D, Kansas City Cardiomyopathy or the Minnesota Living with Heart Failure questionnaires.^{17,48,49}

Iron deficiency can also negatively impact outcomes in CHF. The increased risk of mortality from iron deficiency in studies evaluating CHF patients ranges between 40 and 60%.^{5–7} Iron deficiency in CHF has also been associated with increased hospitalizations, with one study showing that the risk of hospitalization doubled in patients who were not treated for iron deficiency compared with those who were (relative risk [RR] 2.23, 95% confidence interval [CI] 1.59–3.42, $P < 0.01$).⁵⁰ This is further supported by the CONFIRM-HF study, where treatment of iron deficiency with ferric carboxymaltose was associated with a significant reduction in hospitalizations (hazard ratio [HR] 0.39, 95% CI 0.19–0.82, $P = 0.009$).⁴⁶

Notably, the benefit of treating iron deficiency in this setting occurs whether or not patients are also anemic, thus establishing iron deficiency as an independent therapeutic target in CHF.^{51,52} This has led to compulsory iron deficiency screenings in patients with CHF and treatment with IV iron (eg, ferric carboxymaltose) has been recommended.

1.6 | Iron deficiency in chronic kidney disease

The prevalence of iron deficiency in patients with CKD has been reported as ranging from 24 to 85% and, as for CHF, the prevalence increases as CKD progresses.^{4,8} Similar to CHF, iron deficiency in CKD can arise from decreased GI iron absorption, malnutrition and blood loss, which is worsened by chronic inflammation.²⁹ Blood loss in CKD patients can originate from ongoing assessment tests and treatments such as dialysis. Additionally, iron utilization is promoted during the use of erythropoiesis-stimulating agents (ESAs). ESA therapy, while effective in correcting anemia, can further exacerbate iron deficiency, which in turn may result in poor response to ESAs.^{53–56} Unlike cardiologists, nephrologists do not recognize iron deficiency, which is easily treatable, as a distinct entity and still aim to treat iron deficiency in the context of anemia management. Thus, in contrast to CHF, where there is strong evidence that iron deficiency alone impacts the underlying disease, the evidence in CKD is almost non-existent and focuses only on anemia, of which iron deficiency is a major cause.

Anemia in CKD is frequently associated with reduced QoL,⁵⁷ particularly in physical domains such as vitality and energy.⁵⁸ Similar to

CHF, these physical domains appear to play a major role in patient QoL. This is supported by data demonstrating that normalization of hemoglobin (Hb) levels is associated with significant improvements in physical function (SF-36 scores; $P < 0.001$).⁵⁶

At present, the major importance of iron deficiency in CKD is its role in the development of chronic anemia, which is easily correctable. Anemia in CKD is associated with an increased risk of morbidity and mortality.^{59,60} In non-dialysis CKD patients, lower time-averaged Hb levels correlated with a significantly increased risk of predialysis mortality and end-stage renal disease (HR [95% CI] of Hb <11 , 11–12 and 12–13 g dL⁻¹: 2.57 [1.85–3.58], 1.97 [1.45–2.66], and 1.19 [0.86–1.63]; all vs. Hb >13 g dL⁻¹, $P_{\text{trend}} < 0.001$).⁵⁹ In a 5-year observational study, anemia in CKD patients was again associated with increased mortality, regardless of CKD severity.⁶¹ The change from baseline to follow-up in the prevalence of anemia was much higher in patients with CKD stage 2 and 3 who died (stage 2: 42.1%; stage 3: 42.2%) compared with those who were alive (stage 2: 24%; stage 3: 28.3%) at the end of observation.⁶¹ Notably, one study demonstrated that ESA treatment for the correction of anemia in patients with type 2 diabetes and CKD had significant safety concerns, (eg, stroke).⁶² Moreover, no overall cardiovascular, renal or QoL benefits were observed when targeting higher Hb levels compared with the placebo group, who received only iron.⁶² This further supports the point of treating iron deficiency prior to anemia development and requirement for ESAs.

Anemia in CKD patients is often associated with cardiovascular morbidities and can result in increased hospitalization (HR 2.18, CI 1.76–2.70),⁶³ leading to cardio-renal-anemia syndrome. While this overlap between CKD and CHF populations is recognized, the nature of cardiac disease may differ between these groups. As there are differences in the nature of the heart failure, the consequences and treatment of iron deficiency may also differ.

1.7 | Iron deficiency in inflammatory bowel disease

Iron deficiency affects between 13 and 90% of patients with IBD, depending on the population that is studied, eg, in- or outpatients, active or quiescent, as well as severity of the disease.⁴ The main causes of iron deficiency in IBD arise from impaired GI iron absorption due to chronic inflammation, bowel resection (especially in Crohn's disease), disease triggered malnutrition and (mainly chronic) blood loss.²⁷ As with nephrologists, not all gastroenterologists fully appreciate the importance of managing iron deficiency. This may be because the role of iron deficiency anemia in IBD is not fully understood—evidence often depends on the selected patients from tertiary referral centers, including: Crohn's disease and ulcerative colitis; hospitalized patients versus outpatients; or patients with and without surgical interventions.^{27,64} Iron deficiency can be easily corrected before the onset of anemia; however, the current evidence base focuses on iron deficiency anemia and its treatment.²²

Iron deficiency anemia is recognized as one of the most common complications and extra-intestinal manifestations of IBD. However, over 50% of patients who are diagnosed with iron deficiency anemia

TABLE 1 Iron deficiency anemia has more guideline coverage than iron deficiency: summary of iron deficiency diagnostic measures, independent of anemia^{68–85}

			Recommended iron deficiency threshold values independent of anemia		
Professional association	Year	ID/IDA ^a	Serum ferritin (μg L ⁻¹)	TSAT (%)	Additional tests
Chronic heart failure					
ACCF/AHA	2017	ID and IDA	<100 or 100–300	– and <20	–
Canadian Cardiovascular Society	2014	IDA only	–	–	–
European Society of Cardiology	2016	ID and IDA	<100 or 100–299	– and <20	–
French cardiologists	2014	ID	AID <100; FID 100–299	– and <20	–
German commentary for European Society of Cardiology	2013	ID	<100 or 100–299	– and <20	–
National Heart Foundation of Australia and Cardiac Society of Australia and NZ	2011	ID	No threshold recommended	No threshold recommended	–
Spanish Society of Cardiology and Spanish Society of Internal Medicine	2017	ID	<100	or <20	If patients have SF <100 μg L ⁻¹ but TSAT >20%, test for sTfr
Chronic kidney disease ^b					
Canadian Society of Nephrology	2008	IDA only	–	–	–
ERBP	2013	ID and IDA	AID <100	and <20	–
KDIGO	2012	IDA only	–	–	–
KDOQI	2012	IDA only	–	–	–
KHA-CARI ^c	2013	ID	<100; <200–500	<20; <20–30	–
NCGC	2015	IDA only	–	–	–
UK NICE	2015	IDA only	–	–	–
UK Renal Association	2012	IDA only	–	–	–
Inflammatory bowel disease					
Quiescent IBD					
ECCO	2015	ID and IDA	<30	–	–
Portuguese Working Group on IBD	2016	ID and IDA	<30	and <16	CRP assessments
Active inflammatory bowel disease					
British Society of Gastroenterology	2011	ID and IDA	<50 ^d	–	–
ECCO	2015	ID and IDA	<100	–	–
Portuguese Working Group on IBD	2016	ID and IDA	30–100	and <16	CRP assessments

^aGuidelines that only report diagnosis thresholds specific to IDA have been described as 'IDA only'.

^bIncludes both haemodialysis and non-dialysis chronic kidney disease.

^cThese threshold values are based on target ranges for the treatment of iron deficiency.

^dPossibly more, depending on degree of inflammation. ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AID, absolute iron deficiency; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; ERBP, European Renal Best Practice; FID, functional iron deficiency; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anemia; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; KHA-CARI, Kidney Health Australia—Caring for Australasians with Renal Impairment; NCGC, National Clinical Guideline Centre; NICE, National Institute for Health and Care Excellence; NZ, New Zealand; SF, serum ferritin; sTfr, soluble transferrin receptor; TSAT, transferrin saturation.

are not treated.⁶⁵ In a recent survey, it was shown that approximately one-third of patients diagnosed with IBD, who are unsure of their anemia status, do not discuss the possibility of developing iron deficiency anemia with healthcare professionals.²² In this same survey, patients attributed weakness and chronic fatigue to both IBD and iron deficiency anemia.²² Chronic fatigue associated with iron deficiency anemia may be debilitating and has been suggested to be the primary cause of impaired QoL in anemic IBD patients, to the same extent as other symptoms such as abdominal pain and diarrhea.^{22,27,66} Notably, improvements in iron status with IV iron treatment have led to significantly improved QoL in patients with ulcerative colitis and Crohn's disease, according to IBD QoL questionnaire scores ($P < 0.001$) and SF-36 physical ($P < 0.001$) and mental component ($P = 0.024$) scores.¹⁸ Furthermore, changes in Hb levels (but not the activity of the underlying disease) were associated with significant changes in SF-36 ($P = 0.005$)

and IBD QoL questionnaire ($P = 0.009$) scores in IBD patients with iron deficiency anemia.⁶⁷

1.8 | Diagnosis of iron deficiency in chronic inflammatory conditions

Our review of international guidelines available for CHF, CKD and IBD reveals no consensus practical guidance for diagnosing iron deficiency independent of anemia (Table 1). However, only some guidelines recognize iron deficiency as a standalone condition—whether this is through lack of awareness of iron deficiency or an intentional omission is difficult to establish (Table 1). Iron deficiency can be simply diagnosed with routinely available blood tests measuring serum ferritin and transferrin saturation (TSAT).⁸⁶ yet guidelines often lack agreement on test cut-off values for these parameters.⁴ Serum ferritin levels are

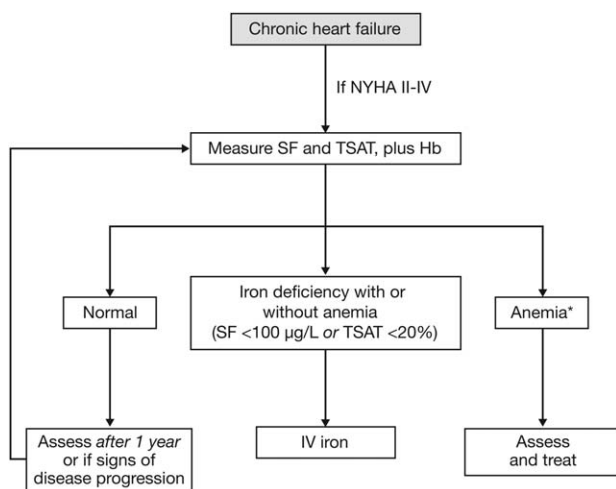


FIGURE 2 Diagnostic algorithm: iron deficiency in chronic heart failure. *Look for other causes of anemia and treat accordingly. Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association; SF, serum ferritin; TSAT, transferrin saturation

sensitive to inflammation and some guidelines recommend assessment of chronic inflammation (according to inflammatory markers such as C-reactive protein [CRP] and erythrocyte sedimentation rate); however, there is little consensus for many conditions on when this should be measured, should it be standard practice for all patients or measured only when serum ferritin is $>30 \mu\text{g L}^{-1}$ or if patients are symptomatic^{68,87}. Moreover, no standard CRP cut-off values are provided; although a CRP level of 5 mg L^{-1} is the most common threshold,⁶⁴ this is not recognized in most guidelines⁶⁸.

1.9 | Expert recommendation

There is little focus in the guidelines on how iron deficiency in the absence of anemia should be diagnosed in relation to the underlying chronic disease. Thus, it is of little surprise that physicians may not prioritize iron deficiency treatment. We wish to propose, based on the literature available, the following consensus laboratory test cut-off values in patients with CHF, CKD or IBD:

Serum ferritin $<100 \mu\text{g L}^{-1}$ or TSAT $<20\%$

If serum ferritin is between 100 and $300 \mu\text{g L}^{-1}$, a TSAT test will be required to confirm iron deficiency

Furthermore, we also propose the following algorithms for the diagnostic workup of iron deficiency in patients with CHF, CKD, and IBD (Figures 2–4). In all conditions, initial workup should incorporate assessment of serum ferritin and TSAT, as well as Hb levels, in order to distinguish between those with normal hematological parameters, those with some form of iron deficiency (iron deficiency: normal Hb and low iron; or iron deficiency anemia: low Hb and low iron), and those with some other form of anemia (where iron levels are normal but Hb is low). In CKD, we must also consider whether the patient is receiving

dialysis (Figure 3A,B). Finally, in IBD, we must further consider whether the underlying condition is in remission or active. For IBD, we therefore also recommend measuring CRP levels or stool markers such as calprotectin or lactoferrin at the time of iron markers and hematological workup, in order to appropriately manage iron deficiency in relation to these results. We recommend a CRP threshold of 5 mg L^{-1} to determine the IBD disease activity. Although laboratory markers are usually sufficient with clinical disease activity markers, other indicators of intestinal inflammation, such as transabdominal ultrasound or endoscopy, may also be used to supplement these assessments.

1.10 | Iron deficiency in high-risk populations with chronic inflammatory conditions

Chronic conditions cannot be viewed in isolation and there will be circumstances where individuals may have further increased susceptibility

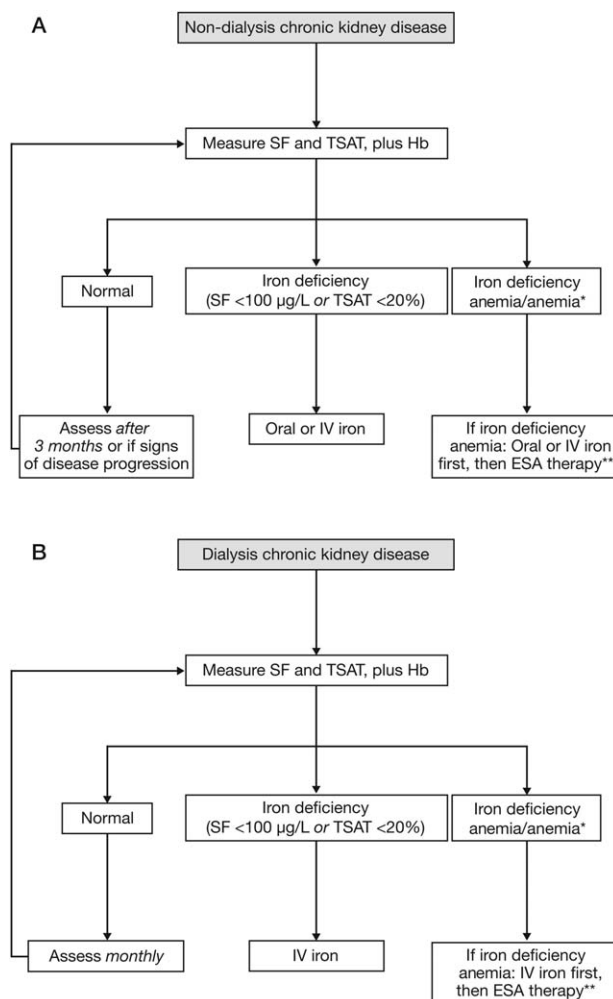


FIGURE 3 Diagnostic algorithms: iron deficiency in (A) non-dialysis and (B) dialysis chronic kidney disease. *If iron stores are normal but Hb is low, look for other causes of anemia and treat accordingly. **When prescribing ESA therapy, iron should always be administered. ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; SF, serum ferritin; TSAT, transferrin saturation

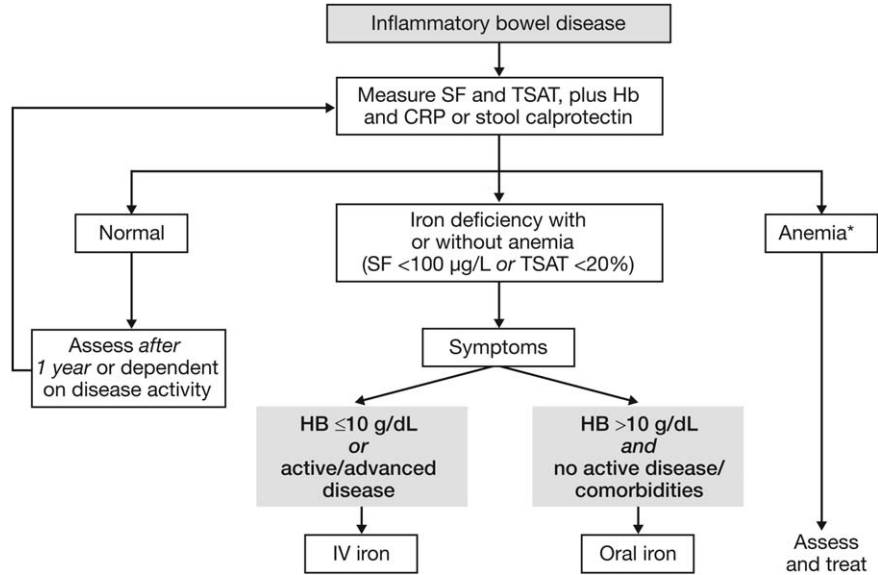


FIGURE 4 Diagnostic algorithm: iron deficiency in inflammatory bowel disease. *Look for other causes of anemia and treat accordingly. CRP, C-reactive protein; Hb, haemoglobin; IV, intravenous; SF, serum ferritin; TSAT, transferrin saturation

to iron deficiency. To optimize outcomes for these patients, risks need to be pre-empted wherever possible. Three important populations to consider among your patients are: women (particularly those who are pregnant or are planning to become pregnant, and those who suffer from heavy menstrual bleeding [HMB]); the elderly; and those undergoing surgery.

Women of reproductive age are one of the most at-risk population groups for iron deficiency anemia. Between 4 and 52% of women of reproductive age are reported to suffer from HMB, with a wide range reflecting disparities between study populations and how HMB is defined⁸⁸ Notably, a recent European study demonstrated that 63% of the participating HMB patients were suffering from iron deficiency or iron deficiency anemia.⁸⁹ Iron deficiency in combination with HMB can have debilitating consequences on the QoL and wellbeing of the

sufferer.^{90–93} Thus, many of these women enter pregnancy with low iron stores and are often already anemic. Approximately 42% of pregnant women worldwide have anemia, with iron deficiency anemia being the primary cause, and this may have a serious detrimental effect on the outcome for both mother and child.^{2,94–96} In pregnancy, iron deficiency anemia is associated with increased maternal morbidity and mortality, possibly due to not being able to withstand the adverse effect of excessive blood loss at delivery and the increased risk of infection.⁹⁶ Iron deficiency anemia also affects the child and has been linked with increased risk of preterm labor and subsequent low birth-weight, and perinatal complications.⁹⁷ Moreover, there is an association between maternal iron status in pregnancy with that of the infant; with infants born to anemic mothers being more likely to be anemic themselves.⁹⁸ Iron deficiency also carries negative long-term impact on the

TABLE 2 Benefits and limitations of oral versus intravenous iron^{20,106–111}

	Oral iron	IV iron
General benefits	<ul style="list-style-type: none">• Ease of use• Lower costs compared with IV iron	<ul style="list-style-type: none">• More efficient and faster than oral iron at increasing iron availability and Hb levels• Effective in the presence of inflammation• Fewer GI side effects than oral iron• Few administrations required to reach target serum ferritin, TSAT and Hb (compared with daily intake of oral iron)• IV administration ensures treatment adherence
General limitations	<ul style="list-style-type: none">• Low intestinal absorption of iron (10–20%)• Low absorption results in slow and limited efficacy• Requires daily intake of up to three equally spaced doses• Decreased iron absorption in inflammatory conditions• Unfavorable (GI) adverse-event profile• Low adherence to treatment• Accidental iron overdose with ferrous salts (eg, ferrous sulfate)^a	<ul style="list-style-type: none">• Requires medical expertise for administration and facilities for cardiopulmonary resuscitation• Potential fatal hypersensitivity may occur• Side effects at injection site may occur• More expensive than oral iron• Complex stability varies between preparations; less stable complexes release larger amounts of weakly bound iron in the blood and can induce oxidative stress if given in high doses

^aThe US Food and Drug Administration has issued a black box warning. GI, gastrointestinal; Hb, hemoglobin; IV, intravenous; TSAT, transferrin saturation.

mother–child relationship and the child's cognitive development, of which the latter has shown to persist for up to 10 years, even after iron repletion.^{95,99,100}

Extra vigilance should also be taken when managing elderly patients. The prevalence of iron deficiency increases rapidly with age, and timely diagnosis and treatment of iron deficiency will substantially improve outcomes and QoL for a population prone to multiple comorbidities.^{101,102} Where surgery is required for your IBD patients, regardless of age, the impact of iron deficiency during procedures that have the potential to result in major blood loss has to be recognized early and proactively managed. An awareness of the substantial impact of pre-operative iron deficiency with and without anemia on morbidity and mortality is increasing, with growing recognition that patient blood management procedures need to be established across all surgical specialties.^{103–105}

1.11 | Management of iron deficiency in chronic inflammatory conditions

Treatment options for iron deficiency fall into two broad categories, oral and IV iron preparations. There are advantages and limitations for each (Table 2) and physicians must decide on the most suitable option on a patient-by-patient basis. Factors that should be considered are: the inflammatory condition of the patient; the degree of iron deficit (ie, the total amount of iron to be replenished); and the time frame that is available or acceptable to achieve adequate iron stores.

Oral iron treatments are the most widely used, largely because of convenience, but there are a number of limitations that impact their effectiveness in patients with chronic inflammatory conditions (Table 2). Oral iron absorption from the ingested amount is low (on average 10%) and even in iron-deficient conditions, upregulation of absorption may be limited.¹⁰⁶ During active inflammation, absorption is further reduced as a result of hepcidin-mediated ferroportin inhibition.¹⁵ Thus, oral iron supplementation may fail to supply sufficient amounts of iron in chronic inflammatory conditions. Recent evidence from the IRON-OUT study further supports the ineffectiveness of oral iron in the chronic disease setting. In this study, no improvement in exercise tolerance or iron stores was demonstrated with oral iron treatment in iron-deficient patients with CHF.¹¹² In the CKD setting, the proportion of anemic patients achieving Hb increase of ≥ 1 g dL⁻¹ at any time was significantly reduced in the oral iron group compared with the IV iron group ($P < 0.001$).¹¹³ Moreover, oral iron treatment has recently been associated with significant changes in the normal gut microbiota, adding to our understanding of how oral iron causes its well-known GI tolerability profile, which is particularly detrimental to IBD patients.¹¹⁴

The alternative solution, IV iron treatment, can deliver a larger iron supply, effectively replenishing iron stores more rapidly than oral iron and, because of the route of administration, bypassing the risk of GI side effects. Many guidelines acknowledge the benefits of IV iron preparations as a valuable option for patients with chronic inflammatory diseases who lack a response to, are non-compliant with, or are intolerant of oral iron treatment, as well as those who have severe iron deficiency and require rapid replenishment of available iron and Hb levels.

However, multiple IV iron preparations are available for which the dosing, infusion times, efficacy and safety profiles can vary. While some products have very little data published demonstrating their benefit-to-risk profile, for other IV iron preparations, such as ferric carboxymaltose, there is a wealth of clinical evidence, including studies in all three chronic inflammatory conditions within the scope of this review; there is a growing evidence base supporting its effectiveness and good tolerability across patient groups.^{32,115–117}

2 | CONCLUSIONS

Iron deficiency is a very common but often overlooked condition, especially in patients with chronic inflammatory conditions. It is a highly relevant comorbidity and accounts for poor outcomes, prolonged hospitalization and poor QoL in this patient population. Here, we have proposed several practical recommendations for the definition and diagnosis of iron deficiency in CHF, CKD and IBD. Based on this definition and diagnosis threshold, simple diagnostic algorithms and management for these conditions have been discussed. The intention of these recommendations is to provide consensus expert opinion where there is variability in the guidelines or gaps in the current evidence base.

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CONFLICTS OF INTEREST

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REFERENCES

- [1] Henriques C. Vifor supports efforts to make public more aware of iron deficiency and its health impact (28 November). IBD News Today 2016. Available at: <https://ibdnewstoday.com/2016/11/28/vifor-pharma-supports-efforts-to-raise-awareness-of-iron-deficiency-in-ibd-patients-others/>.
- [2] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545–1602.
- [3] Nolte E, Knai C, Saltman RB. Assessing chronic disease management in European health systems: concepts and approaches. 2014. Available at: <http://www.euro.who.int/en/about-us/partners/observatory/publications/studies/assessing-chronic-disease-management-in-european-health-systems-concepts-and-approaches>.
- [4] Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr*. 2015;102:1585–1594.
- [5] Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J*. 2010;31:1872–1880.

- [6] Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013; 165:575–582.
- [7] Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol*. 2011;58:1241–1251.
- [8] McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin*. 2004;20:1501–1510.
- [9] Yeo TJ, Yeo PS, Ching-Chiew WR, et al. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. *Eur J Heart Fail*. 2014;16:1125–1132.
- [10] Wessling-Resnick M. Iron homeostasis and the inflammatory response. *Annu Rev Nutr*. 2010;30:105–122.
- [11] Wang J, Pantopoulos K. Regulation of cellular iron metabolism. *Biochem J*. 2011;434:365–381.
- [12] Macdougall IC, Canaud B, de Francisco AL, et al. Beyond the cardiorenal anaemia syndrome: recognizing the role of iron deficiency. *Eur J Heart Fail*. 2012;14:882–886.
- [13] Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016;387:907–916.
- [14] Kassebaum NJ. The global burden of anemia. *Hematol Oncol Clin North Am*. 2016;30:247–308.
- [15] Ganz T. Systemic iron homeostasis. *Physiol Rev*. 2013;93:1721–1741.
- [16] Ganz T, Nemeth E. The hepcidin-ferroportin system as a therapeutic target in anemias and iron overload disorders. *Hematology Am Soc Hematol Educ Program*. 2011;2011:538–542.
- [17] Avni T, Leibovici L, Gafer-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail*. 2012;14:423–429.
- [18] Cekic C, Ipek S, Aslan F, et al. The effect of intravenous iron treatment on quality of life in inflammatory bowel disease patients with nonanemic iron deficiency. *Gastroenterol Res Pract*. 2015; 2015:582163.
- [19] Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372: 1832–1843.
- [20] Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011–1023.
- [21] Weiss G. Anemia of chronic disorders: new diagnostic tools and new treatment strategies. *Semin Hematol*. 2015;52:313–320.
- [22] Danese S, Hoffman C, Vel S, et al. Anaemia from a patient perspective in inflammatory bowel disease: results from the European Federation of Crohn's and Ulcerative Colitis Association's online survey. *Eur J Gastroenterol Hepatol*. 2014;26:1385–1391.
- [23] Himmelfarb J. Iron regulation. *J Am Soc Nephrol*. 2007;18:379–381.
- [24] Ganz T. Iron in innate immunity: starve the invaders. *Curr Opin Immunol*. 2009;21:63–67.
- [25] Cherayil BJ. The role of iron in the immune response to bacterial infection. *Immunol Res*. 2011;50:1–9.
- [26] Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. *Cell*. 2004;117: 285–297.
- [27] Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut*. 2004;53:1190–1197.
- [28] Jankowska EA, von Haehling S, Anker SD, et al. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J*. 2013;34:816–829.
- [29] Tsagalis G. Renal anemia: a nephrologist's view. *Hippokratia*. 2011; 15:39–43.
- [30] Maeder MT, Khammy O, dos Remedios C, Kaye DM. Myocardial and systemic iron depletion in heart failure implications for anemia accompanying heart failure. *J Am Coll Cardiol*. 2011;58:474–480.
- [31] World Health Organization. Iron deficiency anaemia. Assessment, prevention and control: a guide for programme managers. 2001. Available at: http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf.
- [32] Keating GM. Ferric carboxymaltose: a review of its use in iron deficiency. *Drugs*. 2015;75:101–127.
- [33] von Haehling S, Jankowska EA, van Veldhuisen DJ, et al. Iron deficiency and cardiovascular disease. *Nat Rev Cardiol*. 2015;12:659–669.
- [34] Pratt JJ, Khan KS. Non-anaemic iron deficiency—a disease looking for recognition of diagnosis: a systematic review. *Eur J Haematol*. 2016;96:618–628.
- [35] Koduru P, Abraham BP. The role of ferric carboxymaltose in the treatment of iron deficiency anemia in patients with gastrointestinal disease. *Therap Adv Gastroenterol*. 2016;9:76–85.
- [36] Goldberg ND. Iron deficiency anemia in patients with inflammatory bowel disease. *Clin Exp Gastroenterol*. 2013;6:61–70.
- [37] Borgna-Pignatti C, Zanella S. Pica as a manifestation of iron deficiency. *Expert Rev Hematol*. 2016;9:1075–1080.
- [38] Trenkwalder C, Allen R, Hogl B, et al. Restless legs syndrome associated with major diseases: a systematic review and new concept. *Neurology*. 2016;86:1336–1343.
- [39] McDonagh T, Macdougall IC. Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral?. *Eur J Heart Fail*. 2015;17:248–262.
- [40] Brownlie T, Utermohlen V, Hinton PS, et al. Marginal iron deficiency without anemia impairs aerobic adaptation among previously untrained women. *Am J Clin Nutr*. 2002;75:734–742.
- [41] Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr*. 2001;131:676S–688S.
- [42] Jankowska EA, Malyszko J, Ardehali H, et al. Iron status in patients with chronic heart failure. *Eur Heart J*. 2013;34:827–834.
- [43] Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail*. 2011;17:899–906.
- [44] Enjuanes C, Bruguera J, Grau M, et al. Iron status in chronic heart failure: impact on symptoms, functional class and submaximal exercise capacity. *Rev Esp Cardiol (Engl Ed)*. 2016;69:247–255.
- [45] Anker SD, Comin CJ, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009; 361:2436–2448.
- [46] Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36:657–658.
- [47] van Veldhuisen DJ, Ponikowski P, Metra M, et al. *Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure (EFFECT-HF): a Randomized, Controlled Study (NCT01394562)*. New Orleans, LA, USA: American Heart Association 2016 Scientific Sessions; 2016.
- [48] Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Rationale and design of the CONFIRM-HF study: a double-blind, randomized, placebo-controlled study to assess the effects of intravenous ferric carboxymaltose on functional capacity in patients with chronic heart failure and iron deficiency. *ESC Heart Failure*. 2014;1:52–58.

- [49] Enjuanes C, Klip IT, Bruguera J, et al. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol*. 2014;174:268–275.
- [50] Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol*. 2007;50:1657–1665.
- [51] Filippatos G, Farmakis D, Colet JC, et al. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. *Eur J Heart Fail*. 2013;15:1267–1276.
- [52] Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail*. 2016;18:786–795.
- [53] Horl WH. Non-erythropoietin-based anaemia management in chronic kidney disease. *Nephrol Dial Transplant*. 2002;17(Suppl 11):35–38.
- [54] Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol*. 2006;1(Suppl 1):S4–S8.
- [55] Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. *Kidney Int*. 2009;75:15–24.
- [56] Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355:2071–2084.
- [57] Dowling TC. Prevalence, etiology, and consequences of anemia and clinical and economic benefits of anemia correction in patients with chronic kidney disease: an overview. *Am J Health Syst Pharm*. 2007;64:S3–S7.
- [58] Finkelstein FO, Story K, Firanek C, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol*. 2009;4:33–38.
- [59] Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. *Kidney Int*. 2006;69:560–564.
- [60] Singh AK, Szczec L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085–2098.
- [61] Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*. 2004;164:659–663.
- [62] Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
- [63] Thorp ML, Johnson ES, Yang X, et al. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. *Nephrology (Carlton)*. 2009;14:240–246.
- [64] Guagnozzi D, Lucendo AJ. Anemia in inflammatory bowel disease: a neglected issue with relevant effects. *World J Gastroenterol*. 2014;20:3542–3551.
- [65] Ott C, Liebold A, Taksas A, et al. High prevalence but insufficient treatment of iron-deficiency anemia in patients with inflammatory bowel disease: results of a population-based cohort. *Gastroenterol Res Pract*. 2012;2012:595970.
- [66] Jelsness-Jorgensen LP, Bernklev T, Henriksen M, et al. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis*. 2011;17:1564–1572.
- [67] Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2006;12:123–130.
- [68] Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9:211–222.
- [69] KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2:279–335.
- [70] NICE. Anaemia management in people with chronic kidney disease. 2015. Available at: www.nice.org.uk/guidance/ng8.
- [71] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
- [72] Cohen-Solal A, Leclercq C, Mebazaa A, et al. Diagnosis and treatment of iron deficiency in patients with heart failure: expert position paper from French cardiologists. *Arch Cardiovasc Dis*. 2014;107:563–571.
- [73] Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2007;13:1545–1553.
- [74] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart association task force on clinical practice guidelines and the heart failure society of America. *J Card Fail*. 2017. doi: 10.1016/j.cardfail.2017.04.014. [Epub ahead of print]
- [75] National Clinical Guideline Centre (NCGC). Anaemia management in chronic kidney disease. NG8 (update). Commissioned by the National Institute for Health and Care Excellence. 2015. Available at: <https://www.nice.org.uk/guidance/ng8/evidence/full-guideline-70545133>.
- [76] Mikhail A, Shrivastava R, Richardson D. *Clinical Practice Guidelines: Anemia of CKD*. 5th ed., 2009–2012. UK: Renal Association; 2012.
- [77] Magro F, Ramos J, Correia L, et al. Portuguese consensus on the diagnosis, prevention and treatment of anemia in inflammatory bowel disease. *Acta Med Port*. 2016;29:144–156.
- [78] Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut*. 2011;60:1309–1316.
- [79] Levin A, Hemmelgarn B, Culeton B, et al. Guidelines for the management of chronic kidney disease. *CMAJ*. 2008;179:1154–1162.
- [80] Klinger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. *Am J Kidney Dis*. 2013;62:849–859.
- [81] Locatelli F, Barany P, Covic A, et al. Kidney disease: improving global outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*. 2013;28:1346–1359.
- [82] Manito N, Cerqueiro JM, Comin-Colet J, et al. Consensus document of the Spanish Society of Cardiology and the Spanish Society of Internal Medicine on the diagnosis and treatment of iron deficiency in heart failure. *Rev Clin Esp*. 2017;217:35–45.
- [83] Macginley R, Walker R, Irving M. KHA-CARI guideline: use of iron in chronic kidney disease patients. *Nephrology (Carlton)*. 2013;18:747–749.
- [84] Hasenfuss G, Anker S, Bauersachs J, et al. Kommentar zu den Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC) zur

- Diagnostik und Behandlung der akuten und chronischen Herzinsuffizienz]. *Kardiologie*. 2013;7:105–114. [
- [85] Krum H, Jelinek MV, Stewart S, et al. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. *Med J Aust*. 2011;194:405–409.
 - [86] Polin V, Coriat R, Perkins G, et al. Iron deficiency: from diagnosis to treatment. *Dig Liver Dis*. 2013;45:803–809.
 - [87] Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2011;60:571–607.
 - [88] Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. *Expert Rev Obstet Gynecol*. 2009;4:179–189.
 - [89] Fraser IS, Mansour D, Breyman C, et al. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. *Int J Gynaecol Obstet*. 2015;128:196–200.
 - [90] Brownlie T, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. *Am J Clin Nutr*. 2004;79:437–443.
 - [91] Bruner AB, Joffe A, Duggan AK, et al. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet*. 1996;348:992–996.
 - [92] Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. *Value Health*. 2007;10:183–194.
 - [93] Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. *BMJ*. 2003;326:1124.
 - [94] World Health Organization. Worldwide prevalence of anaemia 1993–2005: WHO Global Database on Anaemia. 2008. Available at: http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf.
 - [95] Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. *J Nutr*. 2003;133:4139–4142.
 - [96] Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG*. 2011;118(Suppl 1):1–203.
 - [97] Scholl TO, Hediger ML, Fischer RL, Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *Am J Clin Nutr*. 1992;55:985–988.
 - [98] Colomer J, Colomer C, Gutierrez D, et al. Anaemia during pregnancy as a risk factor for infant iron deficiency: report from the Valencia Infant Anaemia Cohort (VIAC) study. *Paediatr Perinat Epidemiol*. 1990;4:196–204.
 - [99] Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med*. 2006;160:1108–1113.
 - [100] Congdon EL, Westerlund A, Algarin CR, et al. Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years. *J Pediatr*. 2012;160:1027–1033.
 - [101] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *JCO*. 2006;24:2137–2150.
 - [102] Naoum FA. Iron deficiency in cancer patients. *Rev Bras Hematol Hemoter*. 2016;38:325–330.
 - [103] Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet*. 2011;378:1396–1407.
 - [104] Munoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia*. 2017;72:233–247.
 - [105] National Institute for Health and Care Excellence. Blood transfusion: qs138. 2016. Available at: <https://www.nice.org.uk/guidance/qs138>.
 - [106] Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. *Am J Med*. 2008;121:943–948.
 - [107] Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anemia. *Drugs*. 2009;69:739–756.
 - [108] Morris CC. Pediatric iron poisonings in the United States. *South Med J*. 2000;93:352–358.
 - [109] Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. *Pharmaceutics*. 2011;3:12–33.
 - [110] Aapro M, Osterborg A, Gascon P, et al. Anaemia and cancer: oral or intravenous iron? 2012. Available at: <http://orbi.ulg.ac.be/bitstream/2268/153165/1/288.pdf>.
 - [111] Qunibi WY. The efficacy and safety of current intravenous iron preparations for the management of iron-deficiency anaemia: a review. *Arzneimittelforschung*. 2010;60:399–412.
 - [112] Lewis GD, Anstrom KJ, McNulty S, et al. *Oral Iron Repletion Effects on Oxygen UpTake in Heart Failure (IRONOUT HF)*. New Orleans, LA, USA: American Heart Association 2016 Scientific Sessions; 2016.
 - [113] Qunibi WY, Martinez C, Smith M, et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant*. 2011;26:1599–1607.
 - [114] Lee T, Clavel T, Smirnov K, et al. Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut*. 2016;66:863–871.
 - [115] Breyman C, Milman N, Mezzacasa A, et al. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). *J Perinat Med*. 2017;45:443–453.
 - [116] Mahey R, Kriplani A, Mogili KD, et al. Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anemia due to abnormal uterine bleeding. *Int J Gynaecol Obstet*. 2016;133:43–48.
 - [117] Borstlap WA, Buskens CJ, Tytgat KM, et al. Multicentre randomized controlled trial comparing ferric(III)carboxymaltose infusion with oral iron supplementation in the treatment of preoperative anaemia in colorectal cancer patients. *BMC Surg*. 2015;15:78.

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